PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HSM-MC-011	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/IN2004/000155	International filing date *(day/month/year)* 04.06.2004	Priority date *(day/month/year)* 06.06.2003
International Patent Classification (IPC) or national classification and IPC A61K31/435, C07D491/04, C07D495/04		
Applicant CADILA HEALTHCARE LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.01.2005	02.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Deutsch, W Telephone No. +49 89 2399-8281

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2004/000155

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

1-23	as originally filed

   Claims, Numbers

12(part)	as originally filed
1-11, 12(part)	filed with telefax on 23.08.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2004/000155

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 8-10 with respect to industrial applicabilty

   because:

   ☒ the said international application, or the said claims Nos. 8-10 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2004/000155

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

II

The priority of the present claims has been checked.

Claims 1-3 are fully entitled to the earlier priority.
Claims 4 relate to specific compounds not disclosed in the priority document, such that these claims are not entitled to the earlier priority
Claims 5-11 refer partially to claim 4 and thus are only partially entitled to the priority.
Claim 12 is not entitled to the previous priority.

Thus D1 (US 2004/072817 A1 (ANDERSON DAVID ET AL) 15 April 2004 (2004-04-15)), which has a publication date between the priority and filing dates of date is relevant to the examination of novelty and inventive step of claims 4-12, but not claims 1-3.

III

For the assessment of the present claims 8-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 8-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V and VI

Reference is made to the following documents:

D2: EP-A-0 314 362 (PFIZER INC) 3 May 1989 (1989-05-03)
D3: US-a-4 727 080 (SOLER ET AL) 23 February 1988 (1988-02-23)
D4: US-a-4 670 444 (GROHE ET AL) 2 June 1987 (1987-06-02)
D5: EP-a-1 227 096 (SATO PHARMACEUTICAL CO. LTD) 31 July 2002 (2002-07-31)

Novelty

The compounds of the present claims differ from those of D2-D5 through the 6,7-4H-thieno[3,2c]pyridine or 6,7-4H-furano[3,2c]pyridine or 6,7-4H-pyrrolo[3,2c]pyridine groups at the 7 position of the quinoline moiety.

The compounds of claim 4, differ from those of D1, through the presence of the cyclopropyl group at the 1-position.

Inventive Step

Priority valid

The closest prior art is considered to be D4, which discloses quinolinones having antibacterial activity.

The problem underlying the present invention is considered to be the provision of further quinolinone compounds having antibacterial activity.

For the case that NR^1R^2 forms a cyclic group in the compounds of D4, these are only monocyclic groups such as piperazine. D5 discloses oxoquinolinizine substituted by a bicyclic groups, these groups are however structurally too different from the corresponding groups claimed (cf novelty), such that the skilled person would not have arrived at the claimed compounds.

An inventive step may therefore be acknowledged for claims 1-4.

Priority Not Valid

The closest prior art is considered to be D1, since these disclsose in claim 1 generally compounds which differ from those of claim 4 through the presence of a cycloalkyl group rather than a butyl group.

The problem underlying the present invention is considered to be the provision of further quinolinone compounds having antibacterial activity.

It is not considered that the skilled person could have arrived at the specific bicyclic groups in combination with a cyclopropyl group, such that an inventive step can also be acknowledged for claim 4.

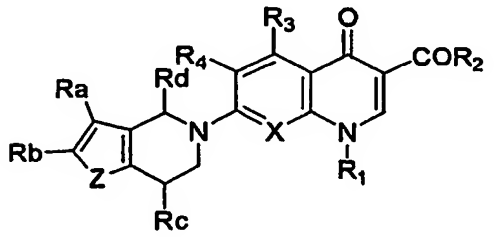
Certain cited documents

The priority of the present application is valid for claims 1-3.

For these claims US 2004/072817 A1 ((ANDERSON DAVID ET AL) 15 April 2004 (2004-04-15)) does not constitute prior art within the meaning of Rule 64.1 (b).

We claim:

1. A compound of formula (I), their stereoisomers, tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutical compositions containing them.



(I)

wherein

R_1 represents hydrogen, linear or branched, substituted or unsubstituted groups selected from (C_1-C_{12}) alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_{12})cycloalkyl; substituted or unsubstituted groups selected from aryl, heteroaryl or heterocyclic groups; R_2 is selected from hydrogen, -OBF_2 or –OR_6,

Where R_6 represents hydrogen, (C_1-C_6)alkyl, (C_3-C_6)alkenyl or (C_3-C_6)alkynyl groups, which may optionally be substituted; R_3 represents H, OH, linear or branched, substituted or unsubstituted groups selected from –O(C_1-C_{12}) alkyl, -O(C_2-C_{12}) alkenyl, -O(C_2-C_{12}) alkynyl, halo, NO_2, CN, or NR'R'' groups, where R'R'' may be same or different and independently represent H, linear or branched, substituted or unsubstituted groups selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6)alkynyl or acyl groups; R_4 represents H or halogen atom; X represents N or C-R_7, where R_7 represents H, -OH, -$(O)_n$(C_1-C_6)substituted or unsubstituted alkyl where n is 0 or 1, -NO_2, -NH_2, -$NHCOCH_3$, -CN, -COOH groups; R_1 and R_7 can be taken together with the atoms to which they are attached to form a cyclic ring, which may optionally be substituted and may also optionally contain from 1 to 3 heteroatoms selected from O, N and S;

Ra, Rb may be same or different and represents hydrogen, halogen, haloalkyl, perhaloalkyl, haloalkoxy, perhaloalkoxy, hydroxy, thio, amino, nitro, cyano, formyl, or substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, linear or branched (C_1-C_{12})alkenyl, linear or branched (C_1-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, (C_1-C_{12})alkenoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, ar(C_1-C_{12})alkoxy, heterocyclyl, heteroaryl, heterocyclyl(C_1-C_{12})alkyl, heteroar(C_1-C_{12})alkyl, heteroaryloxy, heteroar(C_1-C_{12})alkoxy, heterocycloxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, mono-substituted or di-substituted amino, arylamino, aralkylamino, carboxylic acid and its esters and amides,

hydroxyalkyl, aminoalkyl, mono-substituted or di-substituted aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, (C_1-C_{12})alkylthio, thio(C_1-C_{12})alkyl, arylthio, (C_1-C_{12})alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, alkyl hydrazino, alkoxyamino, hydroxylamino, sulfenyl and sulfonyl groups, sulfonic acid , phosphonic acid; R_c & R_d may be same or different and represents hydrogen, substituted or unsubstituted groups selected from alkyl, alkenyl groups; Z represents O, S or NH, which may optionally be substituted;

2. A compound as claimed in claim 1 wherein the substituents on R_1, R_2, R_3, R_6, R_7, R', R'', X, Ra, Rb, Rc & Rd are selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives, phosphonic acid and its derivatives.

3. A compound as claimed in claim 1 wherein R_2 represents -OBF_2 or –OH group.

4. A compound according to claim 1 which is selected from :

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2-nitro-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxy fluoroborate and its pharmaceutically acceptable salts;

1-Cyclopropyl-6-fluoro-8-methoxy-7-(2-nitro-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and its pharmaceutically acceptable salts;

1-Cyclopropyl-7-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxy fluoroborate and its pharmaceutically acceptable salts;

1-Cyclopropyl-7-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-6-fluoro-8-mehtoxy-4-oxo-1,4-dihydro-quinoline-3-carboxy fluoroborate and its pharmaceutically acceptable salts;

1-Cyclopropyl-7-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-5,6,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxy fluoroborate and its pharmaceutically acceptable salts;

1-Cyclopropyl-6-fluoro-8-methoxy-7-(7-methyl-6, 7-dihydro-4H- thieno[3,2-c]pyridin-5-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and its pharmaceutically acceptable salts;
1-Cyclopropyl-6-fluoro-7-(2-hydroxymehtyl-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and its pharmaceutically acceptable salts;
1-Cyclopropyl-7-(2-formyl-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-5,6,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxy fluoroborate and its pharmaceutically acceptable salts;
1-Cyclopropyl-7-(2-nitro-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-5,6,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxy fluoroborate and its pharmaceutically acceptable salts;
1-Cyclopropyl-7-(2-nitro-6,7-dihydro-4H-thieno[3,2-c] pyridin-5-yl)-5,6,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and its pharmaceutically acceptable salts.

5. A composition comprising a compound of formula (I) as defined in any preceding claim, or a therapeutically acceptable salt thereof, and a therapeutically acceptable excipient.

6. A pharmaceutical composition, which comprises a compound as defined in claim 5, and a pharmaceutically acceptable carrier, diluents or excipients or solvate

7. A pharmaceutical composition according to claim 5 and 6, in the form of tablets, pills, capsules, powder, granules, syrup, solution or suspension.

8. A method for treating infections comprising administering a therapeutically acceptable amount of compound of formula (I) as defined in any preceding claim, or a therapeutically acceptable salt thereof.

9. A method for treating an infection caused by gram-positive organisms, gram-negative organisms, mycobacterial infections or nosocomial infections comprising administering an effective amount of a compound according to any preceding claims to a mammal in need thereof.

10. The method as claimed in claims 8 and 9 wherein the compound is administered orally, nasally, parenterally, topically, transdermally, or rectally.

11. Use of the compounds as claimed in any preceding claims or their pharmaceutically acceptable salts for the preparation of medicine suitable for the treatment of infection caused by gram-positive organisms, gram-negative organisms, mycobacterial infections or nosocomial infections

12. A process for the preparation of a compound of formula (I) as defined in claim 1, where all symbols are as defined earlier, and including their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, which comprises: